REMARKS

1. Amendments

Claim 1 has been amended to specify that the methods of the invention relate to suppressing bone resorption in disorders of bone resorption 'characterized by increased bone turnover'. In this regard, claim 2, as filed, has been incorporated into claim 1.

Indeed, excessive bone resorption leads to increased bone turnover and the present invention demonstrates the ability of PlGF inhibition to decrease bone resorption and resulting increased bone turnover, such as indicated in the application at paragraph 6 of US 2005/0175609 A1:

> *Moreover the present invention shows that PIGF antagonists can be used for the manufacture of a medicament for treatment of bone disorders and more specifically for the treatment of conditions* ***where there is an enhanced bone resorption*** *such as for example osteoporosis*. (Emphasis added.)

And at paragraph 4:

> *It is shown that PIGF deficiency results in* ***decreased bone resorption, low bone turnover*** *and increased trabecular bone mass* (emphasis added)

New claims 15-18 find support throughout the specification. For example, new claim 15 finds support at paragraph 36. New claim 16 finds support at paragraphs 61-68, and new claims 17 and 18 find support in the claims as filed.

No new matter has been added by the present amendments.

2. Sequence Rules

Applicants have amended the specification at paragraph 13 to include the reference to the sequence identifier SEQ ID NO: 1.

3. Rejections under 35 U.S.C. §112

Claims 1 and 10 have been amended to recite 'placental', and the rejection of these claims should therefore be withdrawn.

4. Claim Objections

Claims 11 and 12 were deemed improper as failing to limit the subject matter of a previous claim. With regard to claim 11, this objection is respectfully traversed.

Applicants' specification generally refers to diseases of enhanced bone resorption, such as osteoporosis. It is submitted that by referring to diseases such as osteoporosis, characterized by increased bone turnover, the skilled person will understand that the present invention generally relates to metabolic bone disorders with increased bone turnover. Indeed, skeletal homeostasis is dependent upon the delicate balance between bone formation and bone resorption. Metabolic bone disorders are characterized by an imbalance between bone formation and resorption, resulting in an increased bone turnover. While in metabolic diseases such as osteoporosis, this imbalance is caused by one or more factors of bone metabolism being disrupted as a result of hormonal changes, genetic and/or

environmental factors, metastatic bone disorders are caused by a direct interaction of cancer cells with the cells involved in bone formation. Osteoporosis is the best known and most common form of metabolic diseases characterized by an increased bone turnover. However, other forms of metabolic bone disorders were known to the skilled person, such as Paget disease, as evidenced, for example, by the publication of Laurin et al., 2002 (copy enclosed), which in its abstract states:

> *Paget disease of bone is characterized by a focal increase of the bone-remodeling process. It is the second most common metabolic bone disease after osteoporosis.*

Applicants further note that Laurin et al. state, on page 528, left column:

> *The disease is characterized by an increased remodeling process in which abnormal bon resorption remains coupled to new osteoblastic bone formation.*

And on page 528, right column, second paragraph:

> *The primary defect of Paget disease seems to reside in the osteoclast..... Within the pagetic lesion, osteoclasts are large, multinucleated and overactive.*

These statements confirm the recognition of Paget disease at the time of filing as a disorder of bone resorption characterized by increased bone turnover.

Applicants also direct the Examiner's attention to the fact that the data presented in the application demonstrate that there is an unexpected direct effect of PlGF inhibition on osteoclast formation and function. Such data demonstrate that PlGF inhibition provides an efficient method to reduce osteoclast activity and resulting bone resorption. Thus, the skilled person will readily recognized that the use of PlGF antagonists is applicable to any metabolic bone disorder characterized

by an increased bone turnover.

In view of the aforementioned remarks, the objection to pending claim 11 should therefore be withdrawn.

5. Rejections under 35 U.S.C. § 103

The Examiner has indicated that the claims are obvious in view of the publication by Niida et al. (1999). The Examiner asserts

> [I]t would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Niida *et al.* by administering antibodies against VEGF, VEGFR-1 or PIGF with a reasonable expectation of success. The motivation and expected success is provided by Niida *et al.* who teach that mice with osteopetrosis have a severe deficiency of osteoclasts caused by a deficiency in M-CSF (and VEGF can fully compensate for M-CSF) in op/op mice. VEGF causes osteoclastic bone resorption, thus antibodies made against VEGF, VEGFR-1 or PIGF-1 would decrease bone resorption.

Applicants respectfully traverse this rejection.

Niida et al. relate to the fact that VEGF and M-CSF have comparable roles in the regulation of osteoclasts. As indicated by the Examiner, Niida et al. makes use of op/op mice, characterized by osteopetrosis, i.e. a lack of bone resorption caused by deficiency in osteoclasts. This is the result of a lack of functional M-CSF. It is allegedly demonstrated by Niida et al. that VEGF can restore osteoclast function in op/op mice. As indicated by the Examiner, Niida et al. discloses injection of anti-VEGF antibodies in op/op mice, and suggests restoration of osteoclast generation can be inhibited. While assuming that this also applies to the

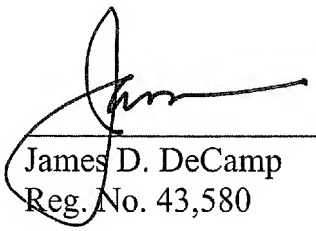
mechanism of bone resorption in osteoporosis, the Examiner provides no indication or reference demonstrating that the underlying mechanism of bone resorption in osteoporosis is comparable to the pathway studied by Niida et al. or that blocking of PlGF activity would have the same effect as direct VEGF inhibition using anti-VEGF antibodies. The 'inverse' reasoning of the Examiner would imply that the excessive osteoclast activity in osteoporosis is attributable to excessive M-CSF and/or VEGF activity, which is not suggested or demonstrated by Niida et al. Moreover, while it is arguably demonstrated by Niida et al. that VEGF can play the role of M-CSF in osteoblast recruitment, this in no way implies the inverse is true, i.e. that inhibitors of VEGF activity can abrogate the eventual effects of e.g. excessive M-CSF. Finally, there is no indication in Niida et al. that the observed effect of VEGF antibodies on op/op mice can also be obtained by PlGF antagonists, making the reasoning even more speculative. Thus it is submitted that the reasoning supporting the obviousness rejection is based on speculation whereby neither the cause of osteoclast recruitment in disorders of bone resorption nor the effect of PlGF antagonists on osteoclast recruitment is in anyway suggested or demonstrated in the cited prior art document.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,



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